MCCC1 and *MCCC2* Gene Analysis in 3-Methylcrotonyl-CoA Carboxylase (3-MCC) Deficiency

CLINICAL FEATURES

Isolated 3-Methylcrotonyl-CoA Carboxylase (3-MCC) deficiency is caused by defects in the mitochondrial 3-MCC enzyme. The phenotype of 3-MCC deficiency is highly variable ranging from severe neurological abnormalities and death in infancy to asymptomatic adults. A severe presentation of 3-MCC deficiency may include a Reye-like illness, ketoacidosis, hypoglycemia, hyperammonemia, psychomotor retardation, seizures, symptoms of cardiorespiratory failure and coma, while a mild presentation can include fatigue and weakness during catabolic episodes or mild developmental delay. Presentations with cardiomyopathy, brain atrophy, and fatty infiltration of liver or muscle may also occur.[1,2] This disorder is the organic aciduria most frequently detected in tandem mass spectrometry-based newborn screening programs. Often, a child with a positive newborn screen will have follow-up testing consistent with 3-MCC deficiency but never present with symptoms of the disorder. In 36 affected individuals identified by a positive newborn screen result, 69% remained asymptomatic at a follow-up of at least 3 years, while the remainder had clinical findings that included various neurological symptoms and acute metabolic decompensation.[3] However the authors note that the neurological symptoms may have explanations other than 3-MCC deficiency.[3] A positive newborn screen in an infant may also lead to the detection of an asymptomatic mother and siblings.

INHERITANCE

Autosomal recessive

GENETICS

The 3-MCC enzyme catalyzes the fourth step of leucine catabolism converting 3-methylcrotonyl-CoA to 3-methylglutaconyl-CoA. 3-MCC is composed of heterodimers of alpha and beta subunits encoded by the *MCCC1* (MCCA) and *MCCC2* (MCCB) genes, respectively. Affected individuals with 3-MCC deficiency have elevated levels of 3-hydroxyisovalerate and 3-methylcrotonylglycine in urine and elevated levels of 3-hydroxyisovalerylcarnitine in blood and urine. These findings are often in combination with severe secondary carnitine deficiency. There does not appear to be an association between the severity of the biochemical phenotype and the clinical phenotype. Clinically affected individuals with 3-MCC deficiency typically have fibroblast enzyme activities less than 2% of controls, although some of these individuals may have activities as high as 12% of controls. The MCCC1 gene, coding for the alpha-subunit, is on chromosome 3q26-q28 and has 19 exons and the *MCCC2* gene, coding for the beta-subunit, is on chromosome 5q13 and has 17 exons.

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the MCCC1and/or MCCC2genes are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

VARIANT SPECTRUM

Variants in *MCCC1* and *MCCC2* occur throughout the gene. A correlation between genotype and biochemical or clinical phenotype has not been observed.[3] The majority of variants that have been identified in *MCCC1* and *MCCC2* are missense, nonsense, frameshift, small insertions/deletions, and spice site changes. Several exon-level deletions have been described in the *MCCC1* gene, to our knowledge no exon-level deletions have been reported in *MCCC2*. Most variants are private.[3]

REFERENCES:

1. Stadler, SL, et al. (2006) Hum Mutat 27(8):748-759 PMID: 16835865.
2.Dantas, MF, et al. (2005) Hum Mutat 26(2):164 PMID: 16010683.
3.Grunert et al., (2012) Orphanet J Rare Dis 7:31 PMID: 22642865.